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Mini-Review

Apoptosis and in vitro Alzheimer disease neuronal models

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Alzheimer disease (AD) is a human neurodegenerative disease characterized by co-existence of extracellular senile plaques (SP) and neurofibrillary tangles (NFT) associated with an extensive neuronal loss, primarily in the cerebral cortex and hippocampus. Several studies suggest that caspase(s)-mediated neuronal death occurs in cellular and animal AD models as well as in human brains of affected patients, although an etiologic role of apoptosis in such neurodegenerative disorder is still debated. This review summarizes the experimental evidences corroborating the possible involvement of apoptosis in AD pathogenesis and discusses the usefulness of ad hoc devised in vitro approaches to study how caspase(s), amyloidogenic processing and tau metabolism might reciprocally interact leading to neuronal death.

Introduction

Alzheimer disease (AD) is the most common human late-onset and sporadic neurodegenerative disorder characterized by global cognitive decline including a progressive loss of memory, orientation and reasoning. The neuropathological hallmarks of AD include synaptic loss and/or dysfunction, diminished neuronal metabolism, senile plaques (SPs), neurofibrillary tangles (NFTs) and loss of multiple neurotransmitter systems.[1]

SPs typically consist of aggregated amyloid beta (Aβ), abnormal neurites and glial cells. The accumulation of Aβ due to a dysregulated proteolytic processing of its precursor molecule, the Amyloid Precursor Protein (APP), exerts a crucial role in neuronal loss or dysfunction through a cascade of events which include oxidative stress, membrane damage, altered mitochondrial metabolism, abortive cell cycle events, Ca^{++} imbalance, protein misfolding, DNA damage/repair and inflammatory processes.[2]

NFTs are intracellular accumulations of cytoskeletal elements, largely made of Paired Helical Filaments (PHF), whose main constituent is abnormally phosphorylated tau. Tangles could potentially damage neurons by disrupting transport of various cellular components, including that of Nerve Growth Factor (NGF)-receptor complex, thus leading to degeneration of the tangle-bearing neurons.[3]

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Thanks to the experimental work carried out in hundreds of laboratories, it has been unequivocally demonstrated that both APP and tau proteins play a crucial role in the onset of AD. Moreover, several strong genetic evidences corroborate the "amyloid cascade hypothesis" according to which Aβ production is the trigger factor affecting downstream tau metabolism.[4] Mutations in several known genes linked to AD familial forms (APP, presenilin-1 or presenilin-2 gene) and genetic or environmental risk factors (Apolipoprotein E 4 variant and metals or pesticides exposure) alter Aβ cellular processing or its properties, leading to an increase of the $A\beta_{42/40}$ ratio or its propensity to aggregate.[1] Moreover, Aβ causes caspases-mediated tau cleavage and hyperphosphorylation by activating specific kinases, thus promoting its aggregation, mis-localization and accumulation with consequent NFTs formation.[5]

Although it is still unclear why specific vulnerable neuronal population, with special emphasis to forebrain cholinergic neurons which provide the majority of cholinergic innervations to cerebral cortex and hippocampus, die in the brain of AD patients, a growing number of studies actually indicate apoptosis as possible initial trigger of the pathology.[6,7]

In this review we will summarize the current findings regarding this hypothesis and we will discuss the convenience of ad hoc devised in vitro models to dissect the single molecular steps linking apoptosis with Aβ production and tau altered processing. A special emphasis will be devoted to analyze the possible crucial role of NGF and other neurotrophins, since the evidences demonstrating its involvement in the onset of AD are becoming conspicuous.[8]

Alzheimer Disease and Apoptotic Events

Several studies presently indicate that apoptosis might occur in, and contribute to, AD onset and progression.[7] Stimuli for apoptosis in AD include increased oxidative stress, dysregulation of ion homeostasis, growth factor deprivation, accumulation of Aβ, metabolic impairment, reduced clearance of toxin, mitochondrial dysfunction, DNA damage, protein aggregation.[9,7] Nevertheless, while the role of apoptosis in in vitro models and transgenic animal models of neurodegeneration has been largely documented, its occurrence and role in human postmortem AD brain is controversial. Despite a growing number of studies underlying caspases and apoptosis involvement in AD, no direct role of apoptotic death in AD etiology has still been proven although the presence of apoptotic bodies, DNA fragmentation, granulated and marginated chromatin and shrunken and irregular cell shapes have been largely reported in tissue sections of brains from affected patients.[10,11] Moreover, an imbalanced level

of some molecular apoptotic markers such as pro-apoptotic (Bax, Bak and Bad) and anti-apoptotic (Bcl-2 and Bcl-x_L) proteins—members of Bcl-2 protein family[12,13]—and the initiator caspases 8 and 9 and the effector caspases 3 and 6 have been also reported in post-mortem brains of AD patients.[11,14-20] Moreover, expression profiling analysis of thousands of genes in brain tissue samples from AD and age-matched control patients has revealed a marked decrease in expression of some anti-apoptotic gene such as NCKAP1.[21] In addition, immunohistochemical and biochemical studies report the presence of active caspase(s) and caspase-cleaved substrates in neurons, around senile plaques and neurofibrillary tangles[10,11,22,23] and also in postsynaptic densities.[24] Both caspase-cleaved APP and activated caspase 3 have been shown to be present and associated to granulovacuolar degeneration, a diagnostic AD neuropathological sign in brains of affected patients.[25] Finally, a marked co-localization of pathological hyperphosphorylated tau, cleaved caspase-3 and caspase-6 have been recently reported in TUNEL-positive neurons in the brainstem of AD patients.[26]

Caspases and APP. Caspases have a direct role in amyloid precursor protein (APP) processing and in the biogenesis of Aβ peptide species.[27] Particularly, the C31 C-terminal peptide obtained by caspase-3 mediated APP cleavage seems to mediate apoptosis by transcriptional regulation of some genes.[28] Caspase-3 mediated APP cleavage also stabilizes BACE—the β-secretase enzyme initiating the APP cleavage to produce Aβ peptide—which accumulates in endosomes, where increases Aβ production.[29]

Exposure of cultured cortical neurons to Aβ or infection of rat hippocampal neurons with APP-expressing adenovirus which causes an Aβ accumulation, induces activation of capsase-3 and apoptosis,[30-33] suggesting that caspase(s) not only participate in the generation of Aβ but they may also directly mediate its toxic effect on neuronal survival.[34]

As will be discussed below, APP-derived toxic peptides may not only originate by apoptosis activation but may also be responsible of it in viable neurons. Thus, APP-derived Aβ peptides can activate caspases through the extrinsic pathway, implicating binding of extracellular Aβ to cell sites, while other studies suggest that the intrinsic pathway may be more relevant.[35] Intracellular accumulation of Aβ in endosplasmic reticulum or endosomes may activate apoptotic mechanism(s) through the unfolded protein response (URP) or endoplasmatic reticulum stress.[36] Alternatively, intracellular Aβ may bind to alcohol dehydrogenase within mitochondria and activates apoptosis causing mitochondrial stress.[37] Interaction of Aβ with mitochondrial Cyclophilin D causes synaptic damage observed in AD and absence of Cyclophilin D protects neurons from Aβ- and oxidative stress-induced apoptotic cell death.[38] Aβ 1–42 also impairs proteasome activity and Aβ immunotherapy rescues the proteasome dysfunction reported in 3X transgenic AD animal models thus confirming that its intracellular accumulation alters the ubiquitin-proteasomal system in vivo.[39] Aβ upregulates the intracellular levels of E2-25K/Hip-2, an E2 ubiquitin-conjugating enzyme, which stabilizes endoplasmic reticulum (ER)-resident caspase-12 protein by inhibiting proteasome activity.[40]

Pharmacological or molecular inhibition of particular members of the caspases family, such as caspase 2, 3, 8 and 12 has been reported to offer partial or complete protection against Aβ-induced apoptotic cell death in vitro.[41-45]

As far as the effect of caspase(s) inhibition on APP metabolism in cellular and animal models, it has been reported that specific down-regulation of caspase-6 in human primary neuronal cultures prevents serum-deprivation mediated Aβ increase, as well as in vitro cell death.[46] In a similar fashion, IETD, a caspase III inhibitor including caspase-6, -8 and -9 prevents APP cleavage in staurosporine-induced cell death in COS transfected cells.[47] In agreement with previous in vitro experimental data, caspase inhibition in vivo by bafilomicin, a pan-caspase(s) inhibitor, abolishes brain trauma-induced increase in Aβ and reduces neuronal degeneration in hippocampus of injected mice.[48] Finally, it is noteworthy that in vivo inhibition of cathepsin B improves memory and synaptic transmission in transgenic mice over-expressing APP, interfering with amyloidogenic APP processing.[49] On the contrary, calpain inhibition is also protective in vivo against cognitive loss in another AD animal model-APP/PS1 mice- by upregulating the phosphorylation levels of the transcription factor CREB (cAMP Responsive Element Binding Protein) without any significant change in Aβ peptides levels.[50]

Caspases and tau. Studies from cellular and animal models indicate that caspases have also been implicated in mechanisms of tau-mediated neurodegeneration in AD.[51,52] According to this hypothesis, Aβ peptide promotes neuronal pathological tau filament assembly by triggering caspases activation leading to tau cleavage.[53] This event, in turn, generates a proteolytic products that assemble more rapidly and extensively into tau pathological filaments.[54,55] Aberrant activation of caspase(s), following apoptotic stimuli or neurodegenerative insults, may produce one or more toxic NH_2-tau fragments, that further contribute to propagate and increase cellular dysfunctions in AD.[56,57] Colocalization of hyperphosphorylated tau and active caspase-3 and 6 has been recently detected in brainstem of young and old AD patients.[26] The finding that the rTg4510 tau transgenic mouse shows caspase-3 activation provides additional supporting evidence linking caspase-3 and tau-mediated neurodegeneration.[58] Caspase-9 activation and caspase-cleaved tau forms have been documented in AD hippocampal brain sections.[18] Finally over-expression of Bcl-2 in a triple transgenic Alzheimer mouse model harboring PS1(M146V), APP(Swe) and tau(P301L) transgenes limits caspase-9 activation, attenuates the processing of APP and tau thus reducing the number of NFTs and extracellular deposits of Aβ associated with the progression of this disease.[59]

It remains to be determined if frank apoptosis is a necessary and early event in the neurodegeneration. According to this view, a positive feedback loop in neurodegeneration would be activated whereby caspase(s) generate Aβ, which in turn exerts a noxious action on tau proteins and further activates caspase(s) in neighboring neurons eventually dying by apoptosis. In this context, other modes of cell death could contribute to neuronal loss in AD[60] and other proteases, such as calpain and cathepsin, can be also directly or indirectly activated by caspases during apoptosis.[61] Finally, an intricate cross-talk between these proteases systems has been reported during apoptosis of neuronal cells.[62] Thus, although other caspase-independent pathways may contribute to the AD progression, the in vivo treatment with specific caspase(s) inhibitors, which are able to penetrate the blood-brain barrier, may still offer an useful and alternative therapeutic strategy to delay selective neuronal loss associated to such neurodegenerative disease.

The Cerebellar Granule Cells (CGC) Model

A decade ago, our research group hypothesized a possible tight link between improper activation of apoptosis and events related to AD. Cerebellar Granule Neurons (CGNs) from 8 days old rat require depolarizing potassium concentration (25 mM K^+) for an optimal survival, when explanted in vitro. Upon reduction of extracellular potassium concentration to a more physiological concentration of 5 mM, these neurons progressively undergo apoptosis[63] which is largely blocked by neuroprotective agents able to increase calcium influx.[64] It has been hypothesized that in vitro depolarizing conditions are necessary to maintain intracellular high levels of free calcium, thus mimicking the in vivo situation of continuous electrical stimulation related to the developmental establishment of excitatory synapses originating from mossy fibers.[9,65] The apoptotic process, as well as nuclear and mitochondrial damage, are reversible up to 4–8 hours of induction suggesting that no rescue is possible even if CGNs are returned to high K^+ medium.[66,67] Activation of caspase-3 has been reported after serum/K^+ starvation[68] and cell death is attenuated by the selective caspase-3 inhibitor z-DEVD-fmk;[69,70] although the main effect of such caspase is on DNA fragmentation and chromatin condensation rather than preventing apoptosis.[71] Such conflicting data may reflect the finding that neuronal apoptosis triggered by potassium reduction involves a more intricate caspase(s) activation cascade[72] and a cross-talk between caspase(s) and other protease(s) further complicates the death signaling.[73-76] Neurotrophin and physiological neuropeptides, such as IGF, bFGF, BDNF, PACAP, SP and cAMP[63,64,76-79] also exert their protective action in this neuronal paradigm through different mechanism including the activation of PI3-kinase/Akt pathway;[76,78,80,81] the stimulation of PKA and/or MAP kinases signaling.[82,83]

We have been reported that the pro-apoptotic shifting to a low potassium medium activates an amyloidogenic process, which rapidly and irreversibly leads to an unbalance between the "physiological" α-secretase-mediated pathway and the β-α-secretase mediated increased production of Aβ.[84] Moreover, the monomeric and oligomeric forms of 4-kDa Aβ are significantly higher in depolarization-stimulated secretion compared with controls. Such increments are paralleled by a corresponding increase of the β-APPs/α-APPs ratio in apoptotic secretion, without any significant change of intracellular full-length APP levels. An interesting aspect of such a process is that the released pool of Aβ may activate a toxic loop that further accelerates and propagates the process of neurodegeneration, affecting neighboring healthy neurons. Indeed, co-incubation of apoptotic cultures with antibodies directed against Aβ significantly slows down the extension of cell death and quantitatively increases the neuronal survival rate by approximately 50%,[85,86] thus suggesting that Aβ peptides may act as soluble and diffusible apoptotic death mediators.

Contextually to the significant increase of amyloidogenic metabolism of APP, also tau undergoes post-translational modifications. After 6 h of potassium deprivation, a change in tau phosphorylation state and caspase(s) and calpain-mediated cleavage occurs in concomitance with a progressive disassembly of cytoskeleton, eventually leading to the generation of a 17 kDa fragment which accumulates in the perikarya of dying cells.[73] Furthermore, following the apoptotic trigger, a reactive oxygen species (ROS) production and progressively reduced mitochondrial function also contribute to neuronal damage.[87,88] Superoxide dismutase, N-acetyl-L-cysteine and other free radical scavengers partially protect CGNs form death, improving mitochondrial energy metabolism.[89,90]

The bulk of studies on CGNs, apoptosis and events related to AD prospected a first, consistent positive answer to their possible link. Nevertheless, the observation that these neurons are not the most vulnerable population affected in AD and that few clinical signs of cerebellar anatomopathological dysfunction have been reported in AD patients leaves room for some criticisms about its fully usefulness as in vitro model for this human neurodegenerative disease.

NGF-Deprived PC12 and Hippocampal/Cortical Neuronal Models

NGF (Nerve Growth Factor) is the first neurotrophin to be discovered and is not only endowed with the property of inducing growth of nerve fibers in target neurons, but also of supporting their life via its antiapoptotic action[91] Numerous in vitro and in vivo data suggest a tight causal relationship between an imbalance in NGF receptor signaling, the activation of amyloidogenic pathway and altered tau metabolism in onset and progression of AD-like neurodegeneration.

TrkA, the high affinity NGF receptor, has been found decreased in the basal forebrain[92-97] and in the cortex.[98-100] A switch from TrkA to p75, the low affinity death receptor, it has been described during neuronal aging resulting in increased amyloidogenic processing of APP.[101-103] p75NTR expression has been directly linked to changes occurring in AD,[104] including the death of basal forebrain neurons,[105,106] hypothesized to occur through a direct binding of oligomeric Aβ1-42 peptides to p75.[103,107,108] Moreover, some evidences have previously showing a transcriptional p75-mediated regulation on the APP promoter leading to an increase of secreted amyloid precursor protein (sAPP)[109,110] in neurons.

Several studies report a regulative role of NGF on tau phosphorylation. Stimulation of undifferentiated PC-12 with NGF causes a dephosphorylation of tau proteins,[111] although an increase of Gsk3β-mediated tau phosphorylation has also been observed. Interestingly, this tau phosphorylation at defined sites might be required for proper anterograde organelle/mitochondrial transport in differentiated cells.[112] On the other hand, NGF deprivation in differentiated PC12 induces apoptosis and hyperphosphorylation both of tau and membrane-bound high molecular weight (HMW) tau, especially in the neuritis. These changes are accompanied by an impairment of its microtubule binding ability and a marked decrease of its solubility. However, in the last stages of apoptosis, tau is dephosphorylated in dying neuronal PC12.[113,114] In addition, in this apoptotic neuronal model, NGF deprivation also causes an early, caspase-mediated tau cleavage at NH_2 domain with the appearance of the 20–22 kDa tau fragment[115] which has been previously demonstrated to be markedly neurotoxic in vitro when overexpressed in primary neuronal cultures.[116] NGF might control the endogenous tau protein levels, regulating its metabolism via proteasomal degradation, as demonstrated by NGF-dependent ubiquitination of tau in cultured cells.[117] Finally, several evidences support the hypothesis that the role of tau in axonal transport might affect NGF-TrkA signaling in vivo. Indeed, experimental data from retrograde labeling of basal forebrain neurons after injection of fluorogold into multiple sites in cortex and

hippocampus, report that an altered compartmentalization of phosphotau, GSK3 and TrkA immunoreactivity may be responsible for the failure of axonal trafficking and lack of trophic support in aged cholinergic cells.[118,119]

The hypothesis that a chronic NGF deprivation may be one of the factors involved in the etiology of sporadic forms of AD is validated by the findings that acute treatment with NGF or acetylcholine esterase (AChE) inhibitors, such as ganstigmine and donepezil, rescues the cholinergic and behavioral deficit in AD11 mice. These mice are an in vivo AD transgenic model, in which the phenotypic knockout of NGF is achieved by the expression of recombinant neutralizing antibodies.[120,121] Finally, clinical encouraging data from ongoing gene therapy trial using NGF-grafted autologous fibroblasts injected into the basal nucleus of Meynert (nbM),[122] further validate the rational for the therapeutic administration of human recombinant NGF in AD patients.[123]

In view of these findings, we carried out a set of experiments in NGF-deprived differentiated PC12 cells[124,115] and described the crucial steps linking NGF withdrawal, activation of amyloidogenesis, tau truncation and caspase(s)-mediated execution of neuronal death. These studies have been replicated in primary hippocampal and cortical neurons showing that, upon NGF removal, the amyloidogenic pathway is activated with consequent intra and extracellular accumulation of Aβ peptides and apoptotic death. The overproduced Aβ is partly released in the culture medium, where it aggregates to form structures largely reminiscent of those forming senile plaques, and in part aggregates within neurons. All these events are prevented by β and α secretase inhibitors, by antibodies directed against Aβ peptides, or by partial silencing of APP mRNA, whereas they are mimicked by Aβ 1–42 peptide exposure. Conversely, neurons deprived of serum largely die but, although the amyloidogenic pathway is activated, the exposure to anti Aβ antibodies does not protect from apoptotic death, further suggesting that the activation of amyloidogenesis following NGF withdrawal is not a simple consequence of an apoptotic trigger but it is strictly related to lack of NGF supply.[125]

In the same experimental model we have also demonstrated an early involvement of tau protein which, under NGF deprivation, undergoes GSK3β mediated hyperphosphorylation at pathognomonic amino acids such as Ser 262 and Thr 231, and is subsequently degraded generating a toxic NH-2-derived 220 amino acid peptide.[116] Such tau hyperphosphorylation, as well as apoptotic death, is blocked by Aβ antibodies or by specific β and/or α-secretases inhibitors and is mimicked by Aβ 1–42 peptide, suggesting that Aβ species are the initial trigger. Tau subsequently detaches from microtubules, thus shifting the equilibrium toward its disassembled state and indirectly affecting the whole axonal transport, eventually leading to apoptotic death (Amadoro et al. submitted). Once tau is displaced from microtubules, it would be further phosphorylated at other fibrillogenic site and/or cleaved by proteases (i.e., caspase(s) and calpain), causing disruption of microtubule transport along axons and consequent synaptic dysfunction. All these events are summarized in the Figure 1.

To our knowledge, the NGF-deprived hippocampal culture is presently the only in vitro model whereby both APP, tau altered processing and apoptosis, have been investigated together under strictly controlled conditions. Regarding the direct role of caspases

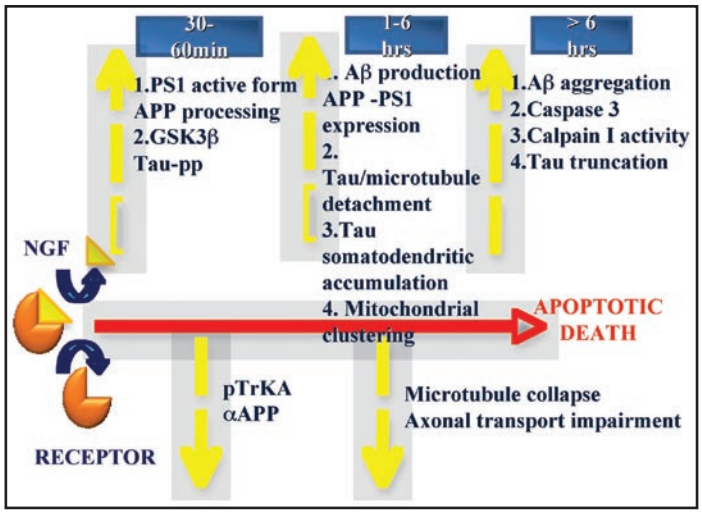

Figure 1. Schematic representation of the apoptotic mechanisms by which the interruption of NGF signaling affects APP processing and Tau metabolism in hippocampal neurons. For more details *see text*.

in neuronal in vitro models whose viability is strictly dependent on NGF, an involvement of such proteases in apoptotic cell death caused by NGF deprivation[126,127] and in the p75-mediated cell death caused by exogenous addition of Aβ to neuroblastoma cells[128] has been largely documented. The studies performed in NGF-deprived PC12 cells show that, among all caspase(s) inhibitors tested, only blockage of executor caspases 2, 12, 6 and 8 exerts an almost total protection from death and from Aβ production, whereas inhibition of effector caspase 3 does not exert a similar action.[124] In a similar fashion and in agreement with others,[129,130] treatment with Z-DEVD-fmk, a specific inhibitor of caspase-3 only partially rescued hippocampal neurons from death, probably because this protease is not activated at early times upon NGF withdrawal in this neuronal paradigm (Amadoro et al. submitted). On the contrary, pharmacological inhibition of caspase 3 markedly inhibited caspases-mediated tau cleavage, without any significant effects on GSK3β-mediated tau hyperphosphorylation (Amadoro et al. submitted). Moreover, the finding that the general cell-permeable caspase inhibitor z-VAD does not significantly affect ThT-positive Aβ structures production in NGF-deprived PC12, whereas partially rescues cells from apoptotic death,[124] delineates a complex chain of events between NGF withdrawal, Aβ production, apoptosis and tau modifications. As mentioned above, the causal and temporal relationship between caspases-mediated cell death and APP processing appears cell-specific and signaling-dependent and probably initiates a toxic cycle of cellular Aβ production/neuronal loss, which is difficult to elucidate in its actual sequence. Thus, although elevated Aβ may lead to apoptotic cell death after injury or disease and caspase(s) inhibition may protect against this event, a causal relationship could not be proven as blockade of caspase(s) might also prevent tau modifications and cell death unrelated to Aβ toxicity. Further investigations aimed at selectively reducing Aβ levels, without targeting caspase(s) activity (i.e., by directly altering α, β and/or α secretase activity), will provide additional insights into this cascade to definitively establish if apoptosis is the primary cause of Aβ production/tau modification or is it a sort of downstream consequence, eventually ending in cell death.

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